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Novel Diastereoselective Routes for the Synthesis of the Ambergris Ketals

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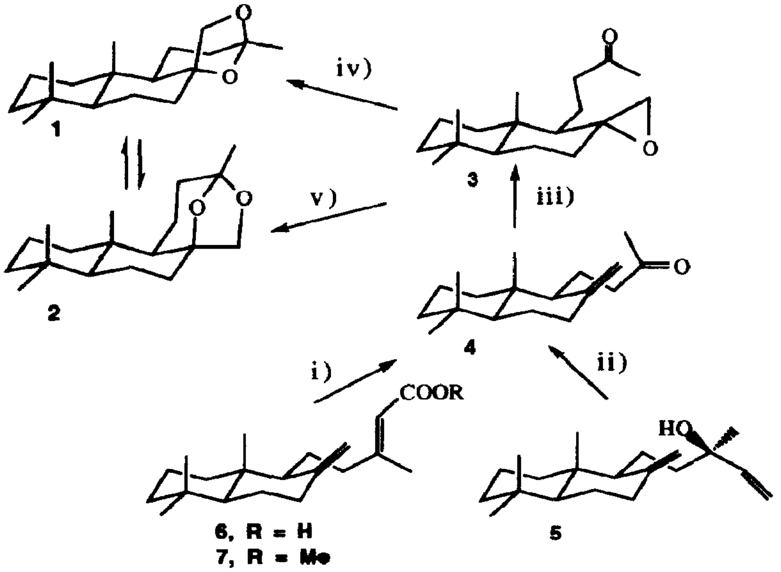
Abstract: New processes have been developed which allow the stereoselective syntheses of the ambergris ketals 8α,13;13,17-diepoxi-14,15-dinorlabdane **1** and 8β,13;13,17-diepoxi-14,15-dinorlabdane **2**, through selection of the appropriate catalyst for the δ,ε-epoxycarbonyl rearrangement of the key intermediate **3**, which is, in turn, obtained by controlled oxidation of anticopalic acid **6**.

The intense fragrance[1] of unequalled tenacity produced by mixtures of the ambraketal **1** and the iso-ambraketal **2** was first described by Jeger *et al.*[2] and is of considerable value to the perfumery industry. Interestingly however, in terms of structure activity relationships,[3] it is important to recognise that ketal **1** is responsible for the strongly odoriferous woody note, while ketal **2** is odourless but fixative.[4] At the present time, in spite of considerable synthetic effort, the development of a commercially viable hemisynthetic route for clean stereocontrolled elaboration of either the desirable spiroketal unit present in ambraketal **1** or its diastereomer **2** remains a challenging objective.[5-9]

As part of a programme to develop potential industrial applications for readily available labdane diterpenoids, we now describe the development of the short and highly efficient sequence outlined in Scheme 1.

The most important element in our strategy lay in the conviction that, since a wide variety of reagents, conditions and mechanistic pathways could be envisaged for the δ,ε-epoxycarbonyl rearrangement of the key intermediate **3**, it should be possible to channel a sufficiently fast reaction under kinetic control to afford either **1** or **2**, prior to further equilibration of these products.

Our first objective however, was to streamline the efficiency of the oxidative degradation leading to the known[10] 14,15-dinorlabdan-8,17-en-13-one **4** using manool **5** as starting material. In this respect, a modification of the method of Ogino *et al.*,[11,12] using anhydrous permanganate in the presence of a phase-transfer catalyst led to a considerable improvement in yield (93%) over the existing literature methods.[10,13] Significantly, we were also able to introduce a new feedstock for this process in the form of anticopalic acid **6**, which can be readily extracted from *Pinus Pinaster* Ait. needles. Permanganate oxidation of **6** or its derived methyl ester **7** once again furnished ketone **4** in high yields (88% from **6**, 82% from **7**). Stereoselective epoxidation of **4** using buffered *m*-chloroperbenzoic acid then furnished the required α-epoxyketone **3**.



i) $KMnO_4$, $C_6H_5N^+(CH_3)_3Cl^-$, CH_2Cl_2, 65% (from 6), $H_2O : C_6H_6$, 82% (from 7), $H_2O : C_6H_6$, 88% (from 6); ii) $KMnO_4$, $(CH_3)_3C_6H_5N^+Cl^-$, $CHCl_3$, 93% or in $H_2O : C_6H_6$, 82% ; iii) aq. $NaHCO_3$ 5%, m-$ClC_6H_4CO_3H$, CH_2Cl_2, 18-20°C, 100%; iv) vermiculite, C_6H_6, 18°C, 100% (C_6H_{14},70%); v) p-$CH_3C_6H_4SO_3H$, $CH_3C_6H_5$, 20°C, 100% ; silica/ alumina/ vermiculite or silicalite, 100°C, 100%.

Scheme 1

Our attention was then directed towards a systematic examination of the δ,ε-epoxycarbonyl rearrangement step. In the first instance, we elected to use a series of Brønsted and Lewis acids under anhydrous homogeneous conditions. The results for a representative set of reactions are shown in Table 1, and reveal several features of interest.

Of the protic acids examined, *p*-toluenesulfonic acid was unique in directing the reaction towards exclusive formation of ketal **2**, while in sharp and unexpected contrast, the use of zinc chloride furnished only the fragrant diastereoisomer **1**. Clearly, in this system, the structure and reactivity of the substrate, the product ketals, and the nature of the acid involved are *all* important in determining a stereochemically clean outcome. From a mechanistic standpoint, a series of elegant synthetic studies by Wasserman[14-16] have led to the rationale that protonation or Lewis acid complexation of the epoxide is followed by stereospecific intramolecular ring opening by the lone pair of the carbonyl oxygen atom with inversion of configuration through a chair like transition state. As shown in Scheme 2, the behaviour of *p*-toluenesulfonic acid is in perfect accord with this hypothesis. Such a model does not however explain the anomalous reaction of zinc chloride, which may conceivably, in this instance, undergo simultaneous coordination to both oxygen atoms and hence direct the approach of the carbonyl group to the developing tertiary centre from the α face as in Figure 2 of Scheme 2. The present case may therefore serve as a caveat to highlight the fact that the total overall structure of the substrate complex with the Lewis acid may play a dominant role in determining the stereochemical outcome.[17,18]

Table I - Intramolecular Ketalization of **3** Using Brønsted and Lewis Acids as Catalysts

REAGENT	SOLVENT	CONDITIONS	TIME	PRODUCT KETALS	
				1 (%)	**2** (%)
p-TsOH	toluene	reflux	30 min	—	100
m-CPBA[a)]	CH_2Cl_2	18°C	7 days	13	72
$BF_3.Et_2O$	Et_2O	0°C	20 min	18	70
CF_3COOD	$CDCl_3$	18°C	20 min	46	54
HCl	THF	reflux	2 hours	50	50
$ZnCl_2$	CH_2Cl_2	18°C	5 hours	75	—

a) Reaction performed on keto-olefin **4** without buffer.[15a]

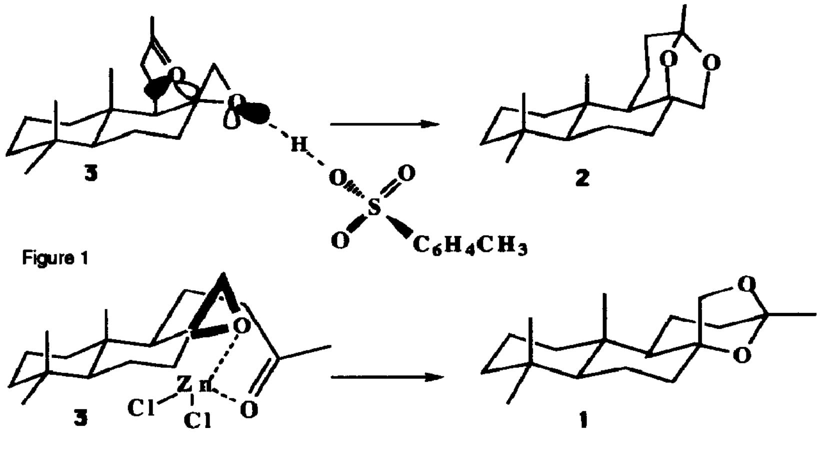


Figure 2

Scheme 2

From an industrial standpoint, it was also of considerable interest to study the epoxy ketone rearrangement under heterogeneous conditions using activated microporous solids.[19] From the results in Table 2, it can be seen that reaction conditions have been developed to produce either one of the ambraketals in a highly diastereoselective manner. The reaction using vermiculite at room temperature in an aprotic solvent is of course particularly relevant. The overall three step process from manool **5** or anticopalic acid **6** using heterogeneous catalysis proceeds in 88-98% overall yield, and is therefore, at the present time, a viable economic route, which may be channelled, as required, to increase the proportion and hence the commercial value of the desirable fragrant ambraketal.[20] It is also of interest to note that the selection of the Lewis acid or heterogeneous support may induce a reversal of stereochemistry from that which is normally observed in the δ,ε-epoxycarbonyl rearrangement.

Table II - Ketalization of **3** With Solid Catalysts[21]

REAGENT AND SOLVENT	**CONDITIONS**	**TIME**	**PRODUCT**	**KETALS**
			1 (%)	**2 (%)**
Zeolites / SiO_2 or Al_2O_3 or Silicalite or vermiculite	100°C	1 hour	—	100
Dry SiO_2 activated with *p*-TsOH / CH_2Cl_2	reflux	4 hours	25	75
DOWEX 50WX-4 / CH_3OH	22°C	1 day	37	63
Nafion-K / CH_2Cl_2	20°C	2 hours	60	30
SiO_2 activated with oxalic acid / CH_2Cl_2	reflux	4 hours	70	25
SiO_2 activated with *p*-TsOH / C_6H_{14}	18°C	3 days	75	25
Nafion-H/Δ / C_6H_{14}	18°C	2 hours	67	13
Vermiculite/ C_6H_6[a)]	18-20°C	3 hours	100	0

[a)] Other solvents were suitable: C_6H_{14}, C_5H_{12}, petroleum ether.

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21. Silica gel MERCK 9385, 230-400 mesh and analytically pure silicalite (a gift from Prof. L. Rees, Dept. of Chemistry, Imperial College, London) were used. The vermiculite used originates from South Africa and contains pyrophilite, SiO_2 39.37%, Al_2O_3 12.08%, MgO 23.37%, Fe_2O_3 5.45%, CaO 1.46%, K_2O 2.46%, Na_2O 0.80%, MnO 0.30 %. The BET area is 7.53 m^2g^{-1} (N_2, after 2 h at 200°C, 0.06 mmHg), and the porosity is 2- 50 nm.

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